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## International collaborative research for pediatric and neonatal lung injury

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## LETTERS TO THE EDITOR

### International collaborative research for pediatric and neonatal lung injury: the example of an ESPNIC initiative to validate definitions and formulate future research questions<sup>☆</sup>

#### Pesquisa colaborativa internacional sobre lesão pulmonar pediátrica e neonatal: exemplo de uma iniciativa da ESPNIC para validar definições e formular questões de pesquisas futuras

Dear Sir,

An interesting review of acute respiratory distress (ARDS) definitions has been recently published in the *Jornal de Pediatria*, focusing on actual needs in terms of research and clinical care of pediatric ARDS.<sup>1</sup>

Unfortunately, timing prevented the consideration of an important step forward in this field. The European Society for Pediatric and Neonatal Intensive Care (ESPNIC), together with some members of the original ARDS Task Force, have set up an international collaborative project to validate the new Berlin definition for infants and toddlers.<sup>2</sup> This project is the first initiative linking different pediatric intensive care units (PICU) in order to reach enough statistical power to address a specific research need. Figure 1 shows the ESPNIC net for this project. Indeed, as Fioretto et al. summarized,<sup>1</sup> no specific pediatric validation had ever been conducted, even though some children were included in the original ARDS definition proposed by Ashbaugh et al. in 1967.<sup>3</sup>

Fioretto et al. described several possible limitations of the Berlin definition: however, some of the points raised by these authors should not be considered as a limitation, since the new Berlin definition is not supposed to be a predictive tool, but rather a framework to define a syndrome for epidemiology, clinical care, and research.

In addition, concerns were expressed regarding the application of the new Berlin criteria to the pediatric population, as there were no children in their original development population.<sup>4,5</sup> This is the reason why the Respiratory Failure Section of ESPNIC started the above-mentioned project to evaluate the reliability of the new Berlin definition in a homogeneous and adequately large pediatric population. The project focused on the early pediatric age (range: 30 days to 18 months), since especially at this age, the syndrome is distinctly different from ARDS in adults.<sup>2,6</sup> In fact, infants and toddlers present peculiarities regarding lung development, respiratory system mechanics, and co-morbidities, which are responsible for the peculiar epidemiology and prognosis of ARDS in these patients.<sup>6</sup>

The main results demonstrated that the new Berlin definition has the same reliability both for the pediatric and adult patients in terms of mortality and need for extracorporeal life support.<sup>2</sup> To aid the clinical application of the definition, a set of chest X-rays with an interpretation guide and a list of ARDS risk factors, as estimated by researchers participating in this collaborative effort, were established. Both are practical tools that have proven to be helpful in clinical practice and research.<sup>2,4,7,8</sup>

However, the ESPNIC collaborative work validating the new Berlin criteria for pediatric ARDS patients has some limitations that have already been pointed out.<sup>2,9</sup> Besides the retrospective character of this pediatric validation study, only one of the several secondary variables that have been tested in adults (i.e. standardized minute ventilation [ $V_{E_{corr}}$ ] = minute ventilation  $\times$  worst  $PaCO_2/40$ ) could be tested.<sup>2</sup> However, other variables (such as lung volume estimation, surfactant amount and activity, biomarkers) could have been tested, and the new Berlin definition could have been more tailored to pediatric patients with an adequate prospective study population. In fact, the Murray lung injury score reviewed by Fioretto et al. has already been modified for pediatric ARDS,<sup>10</sup> but it was never subjected to further validation studies. Finally, other pediatric ages had not been considered: while ARDS in adolescents could be considered as very similar to the syndrome in adults, neonates deserve a specific project to define the syndrome and distinguish it from other forms of neonatal lung injury.

Thus, the ESPNIC collaborative work was an initial and substantial step forward, and disseminated a validated ARDS definition for a particular pediatric population, answering a specific need of pediatric intensivists. Clearly, many other questions remain open, and they can be addressed only with

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**Figure 1** Centers participating in the ESPNIC Respiratory Section project to validate the Berlin definition of ARDS for the early pediatric age. 221 patients were enrolled.

similar international collaborative projects. Such studies are needed, given the complex reality of a syndrome with multiple causes and co-morbidities such as ARDS. Furthermore, it is necessary to study larger pediatric populations in order to reach an adequate statistical power, since ARDS is significantly less frequent in children and neonates than in adult patients.

We are looking forward to proceed with other similar projects in order to answer some of the open questions described above. To do this, and to achieve more representative results, a worldwide collaborative work between the Respiratory Failure Section of ESPNIC and other non-European researchers and clinical centers will be needed.

### Conflicts of interest

The authors declare no conflicts of interest.

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## ARDS definitions in children: one step forward<sup>☆</sup>

### Definições da SDRA em crianças: um passo adiante

Dear Sir,

It was with great interest and pleasure that we read the Letter to the Editor entitled "International collaborative research for pediatric and neonatal lung injury: the example of an ESPNIC initiative to validate definitions and formulate future research questions" by Daniele De Luca et al.<sup>1</sup> The authors commented that the European Society for Pediatric and Neonatal Intensive Care (ESPNIC) published the first validation of the acute respiratory distress syndrome (ARDS) Berlin Definition (BD) in early childhood.<sup>2</sup> Members of the ESPNIC Respiratory Section performed a retrospective international (Italy, Spain, France, Austria, and the Netherlands) multicenter study including children aged between 30 days and 18 months with ARDS according to the American-European Consensus Conference (AECC) criteria.<sup>3</sup> It elegantly addresses our concerns on the applicability of BD in pediatrics when we described the evolution of ARDS definitions.<sup>4</sup>

A time lapse between the two publications prevented exact connections between them; now is the opportunity to do so. The BD<sup>5</sup> for adults and children is an advance, in the sense that ARDS stratification is important for diagnosis and treatment. However, it was obvious that pediatricians working in clinical or basic research needed to validate the new data in children. The work performed by The Respiratory Section of ESPNIC<sup>2</sup> enrolled 221 children, median age 6 months (range 2-13 months), which were categorized according to the two definitions. The authors found very interesting and important results. Applying AECC, 36 children were classified as ALI and 185 as ARDS, with mortality rates of 13.9% and 17.8%, respectively. Conversely, 36 were classified as mild, 97 as moderate, and 88 as severe ARDS

when applying the BD. The BD described the clinical situation better than AECC, with similar results published in adults. Also, the main outcomes were significantly different only for severe ARDS; mortality was 13.9% for mild ARDS, 11.3% for moderate ARDS, and 25% for severe ARDS. They did not find significant differences between mild and moderate classes. However, the inclusion of a severe category in the BD helped to increase its validity. Despite not aimed at identifying risk factors and their association with ARDS, some were presented (sepsis, near-drowning, congenital immunodeficiencies, thoracic trauma, etc.). As expected, they are different than those in the adult population. A properly designed study is therefore necessary to address this issue. The authors concluded that the new ARDS definition correctly adjusts and is able to define the syndrome in its population, subdividing it into mild/moderate and severe ARDS.

Some limitations were addressed. Firstly, the number of patients included was not large. This is a difficulty in all pediatric studies, as populations of children in intensive care are much smaller than those of adults. Secondly, clinical data was not correlated with lung morphology. However, lung biopsy is not commonly performed in critically ill children.

The Brazilian Pediatric ARDS Study Group<sup>6</sup> performed a prospective, multicentre cohort study from March to September of 2013, which aimed: (1) to evaluate the prevalence of ARDS; (2) to determine risk factors for ARDS; and (3) to evaluate whether the use of BD in critically ill children can better discriminate the severity of the disease compared with the AECC definition. The distribution and outcomes of the patients according to the AECC and BD are shown in Table 1.

The BD better discriminates the severity of ARDS in children when compared to the AECC definition, as shown by the incremental increase in mortality rates and reduced number of ventilation-free days in patients with severe ARDS.

In summary, we congratulate De Luca et al.<sup>2</sup> for their timely study, and thank them for their comments. From now on, the pediatric community involved in critical care and emergency medicine, of which we are members, has specific parameters to compare when studying such a serious disease as ARDS in children. Moreover, we look forward to the authors taking a similar initiative in Latin America and other future projects.

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